Immunotherapy for oncogenic-driven advanced non-small cell lung cancers

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Hot Topic

Immunotherapy for oncogenic-driven advanced non-small cell lung cancers: Is the time ripe for a change?

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have been incorporated in the treatment strategy of advanced non-small cell lung cancer (NSCLC) in first- and second-line setting improving the prognosis of these patients. However, the treatment landscape has been also drastically overturned with the advent of targeted therapies in oncogenic-addicted advanced NSCLC patients. Despite ICIs represent an active and new treatment option for a wide range of advanced NSCLC patients, the efficacy and the optimal place of ICI in the treatment strategy algorithm of oncogenic-addicted tumors remains still controversial, as only a minority of trials with ICI enrol oncogenic-addicted NSCLC patients previously treated with standard therapy. Therefore, there are still several open questions about ICI in oncogenic-driven NSCLC, such as the efficacy and toxicities, which need to be addressed before considering treatment with ICI as a standard approach in this population. It is in this framework, we provide a thorough overview on this currently controversial topic.

Introduction

After decades of considering platinum-based chemotherapy as the backbone of treatment for most patients with advanced non-small cell lung cancer (NSCLC), the landscape has been drastically overturned with the advent of targeted therapies and immunotherapy.

Several immune checkpoint inhibitors (ICI) are now considered a new standard of care in lung cancer treatment and have had a dramatic impact on patients outcomes reaching a 5-year overall survival (OS) of 16% [1]. Listed chronologically, nivolumab [2,3], pembrolizumab (restricted to patients with PD-L1 expression (Tumour Proportion Score [TPS]) of at least 1% on tumor cells) [4] and atezolizumab [5] were the firsts ICIs approved in advanced NSCLC, based on their survival superiority over standard chemotherapy in second-line setting. Shortly afterwards, on October 2016 and January 2017, the FDA and EMA endorsed pembrolizumab in previously untreated patients with TPS greater than or equal to 50%, replacing chemotherapy as the first-line treatment of choice in this subgroup of advanced NSCLC patients [6–8]. On top of all, recent data has proven the advantage of new combination strategies based on ICI and platinum-based chemotherapy in both non-squamous [9,10] (with higher benefit among tumors with high TPS) and squamous NSCLC (regardless of the TPS) [11]. But, looking beyond advanced disease, the advantage in progression-free survival (PFS) achieved with durvalumab consolidation in patients with locally advanced disease regardless of histology or PD-L1 expression [12], has also stirred up excitement for the huge potential of immunotherapy in earlier stages of the disease.

Despite immunotherapy represents an active and new treatment option for a wide range of advanced NSCLC patients, the efficacy and the optimal place of ICI in the treatment strategy algorithm of

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oncogenic-addicted tumors remains still controversial, as only a minority of trials with ICI enrol oncogenic-addicted NSCLC patients, such as *EGFR* or *ALK,* previously treated with standard therapy. No doubt about, personalised approach with targeted agents has dramatically improved patients' health outcomes [13–15]. Although only targeted therapies for genetic alterations of *EGFR*, *ALK*, *BRAF* and *ROS-1* are considered so far standard of care, there are many other additional actionable genetic aberrations such as *MET, HER2, RET* or *NTRK* with great potential for target inhibition [16], but despite personalised treatment all patients eventually progress. Therefore, ICI as monotherapy or in combination would be interesting strategies in oncogenic-driven NSCLC patients. However, there are still several questions, such as the efficacy and toxicities, which need to be addressed before considering treatment with immunotherapy as a standard approach in this population. It is in this framework, that we have seen the opportunity of providing a thorough overview on this subject.

PD-L1 expression, Tumor Mutational Burden (TMB) and ICI efficacy

We do now have plenty of data confirming the predictive, albeit imperfect, ability of PD-L1 to identify NSCLC patients with most favourable outcomes to PD-(L)1-blockade [17–19]. Despite its controversial results and constraints based on the responses observed in some negative tumours, PD-L1 expression measured by immunohistochemistry is currently the main scaffold decision-making tool used in clinical practice for selecting those patients deriving most benefit from ICIs at least in first-line setting [19]. Other immunotherapy markers, specifically tumor-mutation burden (TMB) and microsatellite instability (MSI) among others, are also emerging as potentially helpful markers to predict response to ICI. Rational is based on the observation that highly mutated tumors, such as NSCLC [20], are more likely to retain neoantigens which are recognised as foreign by activated immune cells [21–23]. TMB can be determined through whole exome sequencing (WES) or targeted next generation sequencing (NGS) and it is defined as either the total number of somatic mutations in the tumor exome (WES) or the total number of synonymous and non-synonymous mutations per megabase (Mb) present at ≥5% allele frequency in the sequenced tumor genome by NGS (FoundationOne CDx assay). TMB is particularly increased in smokers and noteworthy in metastases as compared to primary counterparts [24,25]. Importantly, TMB and PD-L1 expression appear to be independent predictors of response to ICIs [21,24] as reflected in recent results of first-line phase 3 trials (Checkmate 026 and Checkmate 227) in which progression free survival (PFS) was significantly improved either with nivolumab [26] or nivolumab and ipilimumab [27] as compared to chemotherapy in those patients with high TMB irrespective of PD-L1 expression levels. However, there is still a long road ahead of us towards a proper standardization of TMB calculation and reporting. Indeed, the optimal threshold for determining high TMB is still to be defined. In a discovery set cohort of 64 NSCLC patients treated with ICI, a threshold of TMB ≥ 15 Mut/Mb significantly correlated with longer time on treatment [28], but in the Check Mate 568 phase II trial, TMB ≥ 10 Mut/Mb was identified as the optimal cut-that correlated with ICI benefit [29]. Therefore, TMB should be prospectively validated in a large cohort. Of note, oncogenic addicted tumors are usually correlated with a non- or light-smoking habit, and a recent cohort of advanced NSCLC patients reported no significant differences in PD-L1 expression but significant higher TMB in smoker patients compared to light/never-smoker (8.5 Mut/Mb vs. 4.1 Mut/Mb, p = 0.002), respectively, and TMB [30]. This low TMB is especially significant among the oncogenic alterations strongly related with never-smoker habit such as *EGFR* mutation and *ALK* rearrangements [31]. However, it seems that TMB does not correlate with response to ICI to in driver-mutated tumors, but it should be prospectively validated [32]. Likewise, MSI, a pattern of hypermutation that occurs due to defects in the mismatch repair system, has also been identified as an independent predictor of response to immunotherapy regardless of the cancers' tissue of origin [33]. However, its rarity (only a small fraction of 3.8% of cancers and 1% of NSCLC) [34], impairs its use, at least in NSCLC, as an unique clinical ICI biomarker.

Table 1
Outcomes with ICIs in oncogenic addicted NSCLC patients (ImmunoTarget Cohort [35]).

Genomic alteration	N	RR (%)	PFS* (mo)	OS* (mo)
BRAF	43	24	3.1	13.6
KRAS	271	26	3.2	13.5
ROS1	7	17	NA	NA
MET	36	16	3.4	18.4
EGFR	125	12	2.1	10
HER2	29	7	2.5	20.3
RET	16	6	2.1	21.3
ALK	23	0	2.5	17.0

RR: response rate. N: number. PFS: Progression free survival. OS: Overall Survival.
* From ICI initiation.

Unlike unselected NSCLC, data on ICI activity in patients with oncogenic addiction is much more limited. Recently, the ImmunoTarget cohort [29] has gathered important data. In this multicentric worldwide retrospective cohort, a large set of 551 advanced NSCLC patients treated with ICIs and clustered by driver alterations (271 *KRAS*, 125 *EGFR*, 43 *BRAF*, 36 *MET*, 29 *HER2*, 23 *ALK*, 16 *RET* and 7 *ROS1*) were evaluated for outcomes. ICI were mainly anti-PD1 (92%) given in the first- (5%), second- (42%), third- (26%) or later treatment-lines (27%). For those patients with PD-L1 expression available, 33% (71/214) and 67% (143/214) samples were PD-L1 negative and positive, respectively. With a median follow-up of 16.1 months, the outcomes with ICI in the overall cohort reported response rates (RR) of 19%, median PFS of 2.8 months and an OS of 13.3 months which was similar according to smoking patterns and PD-L1 expression (Table 1). Taken together, this data looks like an accurate replica of the outcomes observed in previous trials with unselected and pre-treated NSCLC patients. However, on closer inspection, it can be noticed that the magnitude of ICI benefit, mainly regarding RR, among the different oncogenic subgroups was distinctly different (Table 1). However, the limited number of patients in some oncogenic alterations does not lead to obtain firm conclusions. The variability of PD-L1 expression [35], the seldom overlaps with high PD-L1 expression (≥50%) [36], the limited TMB and the low occurrence of smoking habits associated to some genomic alterations [24,37,38] (Table 2), as well as differences in tumor microenvironment between different oncogenic alterations and retrospective collection of data may explain the discrepancy in the ICI efficacy in this population. Of note, 57% of patients enrolled on ImmunoTarget cohort [35] had progressive disease to ICI as best response. This percentage is substantially higher than that reported in unselected adenocarcinoma patients in pivotal trials (~45%) [3–5], so, it is unknown whether oncogenic-driver tumors could be at higher risk of developing hyperprogressive disease on ICI, a phenomenon otherwise reported in 14% of unselected NSCLC patients [39].

In another smaller cohort of 52 never or light-smoking NSCLC patients (21% *KRAS*, 12% *EGFR*, 7% *BRAF*, and *RET/HER2/MET*, each 4%), with high PD-L1 expression (≥50% by E1L3N), all treated with anti-PD(L)1 in first- (63%), second- (21%) or ≥third-line (15%), the efficacy measured by RR was 26% with a median duration of response (DoR) of 5.6 months and median PFS and OS of 3.0 and 16.4 months, respectively [30]. Currently, ongoing clinical trials are exploring the use of combination strategies (tyrosine kinase inhibitors or chemotherapy and ICI) in oncogenic-addicted NSCLC patients. However, careful considerations must be made given the increased risk of toxicity described with the use of both concomitant and sequential combinations of targeted agents and ICIs [40].

Table 2
PD-L1 expression and TMB biomarkers among different driver alterations in NSCLC.

Genomic alteration	PD-L1 ≥50% (%)	TMB (median Mt/Mb)
Non-selected	35%	5.7–7.4
KRAS	17%	9.0
BRAF	45% (V600-E > non-V600E)	High TMB (≥20 Mb) in V600-E vs. non-V600E: 20% vs. 0%
MET	44%	3.8–4.5
EGFR	33% to 57.1% (heavily pre-treated)	3.8 (3.6 Mut/Mb for *EGFR* exon 19 deletions, 3.8 for *L858R* and 4.5 for *T790M*)
HER2	13%	5.7
ALK	26% crizo-naíve 17% crizo-resistant	3.1
ROS1	5% (1/19)	3.6
RET	21%	3.3

TMB: Tumor Mutational Burden; Mt: mutations; Mb: Megabase; Crizo: crizotinib.

KRAS mutation

KRAS mutation is the most common oncogenic alteration found in lung cancer with an incidence of approximately 30% in adenocarcinomas [41]. *KRAS*-mutations are ethnic-driven since they are found in only 10% of Asian patients [42] and have a close link with tobacco exposure with an incidence ranging between 25 and 35% in ever smokers and only 5% in non-smokers. In lung adenocarcinoma, most common *KRAS*-mutations occur in codons 12 and 13, being *G12C* transversion among the most commonly mutation reported in approximately 40% of the cases. The fact that no targeted therapy has yet been approved for the treatment of *KRAS*-mutant NSCLC [43] and its strong relation with cigarette smoking, awoke the plausible interest to deeper explore the use of ICI in this subgroup of patients.

PD-L1 expression is significantly increased in *KRAS*-mutant tumors as compared to wild-type counterparts (38.9% versus 16.2%, $p < 0.001$) as well as in *KRAS- G12V* variants as compared to other *KRAS*-mutations (8% for *G12C*, 5.3% *G12D* and 12.9% *G12V*, $p = 0.044$) [44], with high PD-L1 expression (≥50%) in 17% of *KRAS*-mutant patients [45]. Furthermore, median TMB is also higher in *KRAS*-mutant than unselected adenocarcinoma tumors (9.0 mut/Mb compared with 6.3 Mut/Mb) [46]. Despite the unambiguous association with smoking, the immediate impact of *KRAS*-mutation on the effectiveness of ICI in lung adenocarcinomas is more than debatable. In a recent systematic review and meta-analysis of 5 clinical trials involving 3,025 NSCLC patients treated in second line with ICI (nivolumab, pembrolizumab, atezolizumab) [47] although a greater benefit with a 35% reduction in the risk of death was observed in *KRAS*-mutant NSCLC patients (HR, 0.65; 95% CI, 0.44–0.97; $p = 0.03$) as compared to *KRAS* wild-type (HR, 0.86; 95% CI, 0.67–1.11; $p = 0.24$), no statistically significant test interaction differences were noted between *KRAS* status and treatment effect ($P = 0.24$). Hence, the use of *KRAS*-mutation as the sole predictive biomarker for the selection of patients for ICI therapy appears unreasonable. On the contrary, the coexistence of both high PD-L1 expression and *KRAS*-mutation, has been significantly associated with an improved OS ($p = 0.012$), an advantage otherwise not reproduced in the wild-type population ($p = 0.385$) in this study [44]. Among the 271 *KRAS*-mutant NSCLC patients enrolled in the ImmunoTarget cohort, ICIs reported RR of 26%, with a median PFS of 3.2 months and OS of 13.5 months (Table 1). Whereas the levels of PD-L1 expression significantly correlated with an improved PFS ($p = 0.01$), neither the type of *KRAS*-variant ($p = 0.47$), nor the number of previous lines received ($p = 0.66$) had an impact on outcomes [35].

Besides PD-L1 expression, data gathered over recent years has identified distinct molecular features of *KRAS*-mutant tumors co-occurring with other mutations such as the tumor suppressor gene serine/threonine kinase 11 gene (*STK11*) also known as liver protein kinase B1 (LKB1) [48]. The *STK11* is mutated in approximately 15 to 20% of NSCLC and *STK11*/LKB1 function is lost in approximately one-third [49] to 50% [48] of *KRAS*-mutant adenocarcinomas. *STK11* mutations correlate with smoking history [48,49] and, though its prognostic role is still uncertain, it seems that *STK11* loss-of-function might correlate with worse outcomes in advanced NSCLC [48]. Indeed, co-existence of both mutations (*KRAS*-driven, LKB1-deficient) is associated with a higher number of metastatic sites at diagnosis as well as an increased risk for developing brain metastases [49]. This observation might explain the trend toward a detrimental effect on OS described with the concurrence of both mutations [48,49].

Interestingly, inactivation of *STK11* (or its protein product, LKB1) by mutational or non-mutational mechanisms has been associated with an inert or "cold" tumor immune-microenvironment [50]. This observation has also been observed in pre-clinical models, in which *STK11*/LKB1-positive lung adenocarcinoma cell lines are characterized by a low TPS as well as a decrease in the percentage of tumor-infiltrating lymphocytes (TILs) [51]. Accordingly, the co-existence of *STK11* alterations in *KRAS*-mutant lung adenocarcinoma patients treated with PD-1 inhibitors correlates with lower RR (28.6% vs. 7.4%, $p < 0.001$), shorter PFS ($p < 0.001$) and worse OS ($p = 0.0015$) [51], suggesting its nature as a major genomic driver for primary resistance to ICI therapy. Moreover, *STK11/LKB1 de novo* resistance to PD-1/PD-L1 inhibitors is retained even among those PD-L1-positive NSCLC patients, suggesting that their effect is at least partially independent of PD-L1 expression. Therefore, genomic screening evaluation of *STK11*/LKB1 might be useful to enhance the predictive utility of a composite ICI-predictive biomarker panel, together with PD-L1 expression and TMB [52]

EGFR mutation

EGFR mutation is the most common druggable genomic alteration reaching 15% of lung adenocarcinomas in the Caucasian population and in up to 60% of the Asian population. *EGFR*-mutations are more common in never/light smokers and females. First- and second-generation EGFR tyrosine kinase inhibitors (TKI) -erlotinib, gefitinib, and afatinib-, as well as third-generation EGFR TKI -osimertinib- are approved as upfront standard treatments for tumours with common sensitizing *EGFR*-mutations [53,54]. Osimertinib has also been approved for the 60% of patients who develop an acquired resistance *T790M* mutation [55]. Platinum and pemetrexed combination remains the standard of care for those patients without the *T790M* at TKI-progression [56].

There is plenty of evidence that *EGFR*-driven lung tumors drive immune escape by upregulating PD-1, PD-L1, CTL antigen-4 (CTLA-4), and other tumor-promoting inflammatory cytokines and PD-L1 expression can be reduced by EGFR-inhibition in *EGFR*-mutant NSCLC cell lines [57]. However, although PD-L1 expression is higher in *EGFR*-mutant cell lines compared with wild-type counterparts [58] results in the clinic are thus far conflicting with variable expression levels reported in literature, mainly in pre-treated patients. Some recent retrospective analysis have reported lower PD-L1 expression scores in pre-treated *EGFR*-mutant patients, compared to EGFR-wild-type [59], however, contradictory results have been reported in two different meta-analyses [60,61]. It is worth mentioning that there was a huge variety of PD-L1 assays and antibody clones used, challenging its extrapolation of preclinical data into clinical practice. Recently, clinical data from the prospective FLAURA phase III clinical trial in untreated *EGFR*-mutant patients has reported that PD-L1 expression is less common in *EGFR*-mutant than EGFR-wild type samples, particularly in higher thresholds (PD-L1 ≥ 25%: 8% vs. 35%; and PD-L1 ≥ 50%: 5% vs. 28%) [62]. Despite that some retrospective clinical cohorts in *EGFR*-

mutant population have correlated the PD-L1 expression with decreased EGFR TKI efficacy [63], in the FLAURA trial, the PFS benefit with osimertinib compared to standard treatment occurs regardless of PD-L1 status [62]. Other series have suggested the dynamic increase of PD-L1 expression over time [45]. Indeed, PD-L1 expression of ≥1% and ≥50% has been reported in only 24% and 11% of pre-treated *EGFR*-mutant patients [45], rates otherwise much lower that of reported in unselected NSCLC patients (PD-L1 ≥ 1%, ≥50% in 60% and 35% of samples respectively) [4]. On the other hand, although high TPS of at least 50% seldom overlaps with driver genes in untreated *EGFR*-mutant tumours [36] in heavily pre-treated patients higher levels of PD-L1 (≥50%) have been reported in around 33% of patients (18 of 54) [64]. This phenomenon underlines the dynamic nature of PD-L1 expression in *EGFR*-driven tumors and sustains the increased infiltration of CD8 TILs observed within the tumor microenvironment at the onset of resistance [45]. *T790M*-mutation, on the other hand, seems to be correlated to lower PD-L1 expression levels compared to *T790M*-negative resistant tumors (31% vs. 61%, p = 0.0149) [65]. The TMB, as happens in other driven-tumors, is significantly lower than in unselected NSCLC patients (3.8 vs. 6.12 Mut/Mb, respectively, p < 0.0001) [66] and it does not appear to be major different according to *EGFR*-mutation subtypes (3.6 Mut/Mb for *EGFR* exon 19 deletions, 3.8 for *L858R* and 4.5 for *T790M*) [46]. Of note, TMB increases at resistance time (median 6.56 vs. 3.42 Mut/Mb, p = 0.008), and TMB is negatively associated with clinical outcome in *EGFR*-mutant NSCLC patients treated with EGFR TKI [66].

Despite the variable PD-L1 expression and low TMB, several immunotherapeutic approaches have been tested in *EGFR*-mutant patients based on the enhanced susceptibility to immune-checkpoint blockade observed in *EGFR*-mutant mouse models [57], although no signs of synergistic efficacy were noted in co-cultures with combination strategies of *EGFR*-TKIs and ICIs [67].

In a phase II trial in EGFR TKI naïve, PD-L1 positive (≥1%, 22C3 antibody) *EGFR*-mutant NSCLC patients, no signs of activity were reported with pembrolizumab, including those with PD-L1 expression ≥50%, suggesting that first-line treatment with ICI in this subgroup of oncogenic tumors is far less than appropriate. Indeed, three out of the seven patients that were subsequently treated with *EGFR*-TKI experienced grade 3–5 toxicity [68], underlying the potential increased risk of toxicity when combination approaches are performed, even in a sequential manner. Likewise, in second-line setting a meta-analysis reported the lack of OS benefit with ICIs in this population (HR 1.11; 95% CI 0.80–1.53, p = 0.54, interaction p = 0.005) [69]. However, some signs of activity have been reported in some other retrospective studies. Among the 125 *EGFR*-mutant NSCLC patients enrolled in ImmunoTarget cohort, ICIs reported RR of 12%, with a median PFS and OS of 2.1 months and 10 months, respectively (Table 1). Whereas the levels of PD-L1 expression significantly correlated with an improved PFS (p = 0.01), neither the type of *EGFR*-mutation subtype (p = 0.35), nor the number of previous lines received (p = 0.19) had an impact on PFS [35]. In another retrospective Italian cohort enrolling 102 *EGFR*-mutant NSCLC patients treated with nivolumab, the RR was lower in *EGFR*-mutant patients compared to wild-type patients (RR 8.8% versus 19.6%, p = 0.007) but no differences in PFS and OS were observed [70]. The phase II ATLANTIC trial testing durvalumab as third-line treatment included the largest cohort of *EGFR*-mutant patients treated with ICI (n = 98) after progression on EGFR TKI and chemotherapy. According to PD-L1 expression (< 25% or ≥25%), durvalumab achieved a RR of 3.6% and 14.1%, a similar median PFS 1.9 months and a median OS of 9.9 months and 13.3 months, respectively [71,72]. Some other clinical trials (CheckMate 012 [73], CA209-003 [1], CA209-153 [74], KEYNOTE 001 [64] and BIRCH trials [75]) have also enrolled representative cohorts of *EGFR*-mutant NSCLC patients and the efficacy ICI in this population is summarized in the table 3.

On the other hand, data on the activity of ICI in patients with non-classic *EGFR*-mutations is scarce. Compared to classic *EGFR*-mutations, patients with non-T790M exon 20 mutations seem to gain better PFS and OS when treated with ICI (2.9 vs. 1.9 months, HR 0.45, p = 0.002 and NR vs. 11.5 months, HR 0.2, p < 0.001) [76]. However, the limited number of patients included does not lead to obtain firm conclusions.

Despite lack of synergism reported in preclinical models with EGFR TKI and ICI [67], several early phase clinical trials have evaluated this strategy. Design, primary outcome, results and toxicity (≥grade 3) are summarized in table 4. As expected, in TKI naïve patients, ORR was 70–79%, which is comparable to that obtained with *EGFR*-targeted therapy alone in first-line. Likewise, as foreseen by preclinical results, no clear synergistic effect of the combination was observed (Fig. 1). Grade ≥ 3 AE's were common (24–54%) and variable (table 4 and Fig. 1). Of note, the IMPOWER 150, a phase III trial testing the combination of bevacizumab plus carboplatin-paclitaxel with or without atezolizumab in first-line setting, enrolled 70 *EGFR*-mutant TKI-previously-treated advanced NSCLC patients. In the *EGFR/ALK* subgroup the combination arm with atezolizumab significantly improved the PFS compared to control arm, (9.7 vs. 6.1 months, HR 0.59 [0.37–0.94]) as well as OS (not reached vs. 17.5 months, HR 0.54 [0.29–1.03]) but carboplatin-paclitaxel with atezolizumab did not improve OS over control arm (21.2 vs. 17.5 months, HR 0.82 [0.49–1.37]) in this population [10].

Other intervention strategies are to evaluate the combination of ICIs plus chemotherapy in the resistant setting (NCT02864251, NCT03256136, NCT03515837), as well as the combination of ICI and anti-CD73 therapies (NCT03454451) based on preclinical rational sustaining CD73 expression as a biomarker of immune-resistance. Nonetheless, the definitive place of immunotherapy in the therapeutic landscape of *EGFR*-mutant patients remains to be defined.

BRAF mutation

BRAF mutations are observed in 1% to 2% of lung adenocarcinomas [41,77,78], preferentially in non-mucinous mainly micro-papillary adenocarcinomas, although cases have also been reported in sarcomatoid and large cell carcinomas. Unlike melanoma, only half of *BRAF*-mutations found in NSCLC are V600E. Most common clinical features include female gender [79] and smoking habits [80], and outcomes trend to be poorer [81] with lower responses to chemotherapy [41,82]. *BRAF V600E* mutations predict response to *BRAF*-inhibitors such as vemurafenib or dabrafenib [83,84], as well as double *BRAF-MEK* inhibition with dabrafenib and trametinib [85,86], so *BRAF*-mutation screening is currently recommended in clinical practice [16]. Based on the results of the single arm phase II trial with dabrafenib and trametinib combination in first-line setting (RR of 64% and median PFS and OS of 10.9 and 24.6 months, respectively), both the FDA and EMA have endorsed double *BRAF-MEK* inhibition combination as standard treatment in *BRAF*-V600E mutant advanced NSCLC patients [84].

As *BRAF*-mutation is associated with smoking history, the efficacy of ICI in this subpopulation merits undeniably further evaluation. In a recent retrospective cohort of 39 *BRAF*-mutant advanced NSCLC patients (21 *V600E*- and 18 non-*V600E*), high PD-L1 expression levels (≥50% by 22C3 IHQ) were reported in ~45% of patients, with is otherwise higher than that reported in unselected NSCLC patients. In *BRAF* (V600E) tumors, 25% of cases were associated with high TMB (≥20 Mb, by FoundationOne algorithm) compared with 0% in non-*V600E* mutant tumors; and all cases were microsatellite stable regardless of *BRAF*-mutation subtype [87]. In another series, median TMB was higher in BRAF non-*V600E* than in *V600E*, 10.8 Mut/Mb compared with 3.8 Mut/Mb, respectively [46]. Among patients treated with ICIs (N = 22), there were 28% of responses, with a median PFS of 3.7 months and an OS that has still to be reached. Any of the outcome measures (RR, PFS or OS) were found to be significantly correlated with *BRAF*-mutation subtype or PD-L1 expression [87]. However, those patients who received ICIs lived significantly longer than those not

Table 3
Clinical outcome of *EGFR*-mutant tumors treated with immune checkpoint inhibitors in clinical trials enrolling non-small cell lung cancer patients.

Author/Trial	PD-L1 restricted?	Treatment	Total r of ICI patients* *EGFR* wt/ *EGFR* +	ORR (%) for ICI*EGFR* − vs *EGFR* +	DoR in months for ICI *EGFR* − vs *EGFR* +	Median PFS in months for ICI *EGFR* − vs *EGFR* +	Median OS in months for ICI *EGFR* − vs *EGFR* +	Remarks (tox, LTS)
EGFR TKI naive trials								
Lisberg [130]	TPS ≥1%	Pembro	All *EGFR* + 11 (1 false positive)	False positive: response, *EGFR* + 0	False positive: 8.2 *EGFR* no responses	NA	NA	Subsequent TKI: 3/7 patients TRAE gr 3–5
EGFR TKI pretreated/no specific requirements regarding TKI pretreatment trials								
CheckMate 012 ~ [73]	Unselected patients	Nivo	52 31/8	30/14	NR	6.6 vs 1.8	NA	–
CheckMate 012ß [131]	Unselected patients	Nivo + ipi	78 54/8	41/50	NA	*EGFR* − NA *EGFR* + 13.6	NA	–
CA209-003 [1]	Unselected patients	Nivo	129 56/13	19.6/16.7	NA	NA	NA	16 survivors ≥5 years 2 *EGFR* + (exon 20 ins and exon 18 G719A)
CA209-153 [74]	Unselected patients	Nivo	129/12	17/16Δ	NA	NA	NA	–
CheckMate 057 [3]	Unselected patients	Nivo	292 168/44	18/11	NA	For *EGFR* + : HR 1.46 ICI vs chemo	For *EGFR* + : HR 1.18 ICI vs chemo	–
KEYNOTE 001 [64]	Unselected patients	Pembro	550 450/77	21.6/7.8	NA	NA	NA	–
KEYNOTE 010 [4]	TPS ≥ 1%	Pembro	690 581/60	NA	NA	For *EGFR* + : HR 1.79 ICI vs chemo	For *EGFR* + : HR 0.88 ICI vs chemo	–
BIRCHΣ [75]	TC/IC ≥ 5%	Atezo	659 498/45	19/9	NR vs 8.5	5.5 vs 5.5	NR vs 20.1	–
OAK [5,132]	Unselected patients	Atezo	425 318/42	15/5	NA	NA	15.3 vs 10.5 For *EGFR* + : HR ICI vs chemo 1.24	9% of LTS (≥24 months survival) was *EGFR* +
ATLANTIC [71,72]	After amend-ment TPS ≥ 25%	Durva	Cohort 1: 11115 *ALK*/ 97 *EGFR*∞	*ALK*:0 *EGFR*: TPS < 25/TPS ≥ 25% 3.6/14.1	*ALK*: no responses *EGFR* + 7.4	Cohort 1: 1.9	Cohort 1: 9.9–13.3	–
Large retrospective series								
Italian EAP [70]	Unselected patients	Nivo	1588 1293/102	19.6/8.8	NA	3.0 vs 3.0 (HR 1.38)	11.0 vs 8.3 (HR 1.11)	–
Mazieres, 2018 ImmunoTarget [35]	Unselected patients	All ICI	550 NA/125	Total 19.0/*EGFR* 12.0	NA	Total 2.8 *EGFR* 2.1	Total 13.3 *EGFR* 10.0	–

Abbreviations: PD-L1: programmed death ligand1; nr: number; ICI: immune checkpoint inhibitor; EGFR: epidermal growth factor receptor; wt: wildtype; DoR: duration of response; vs: versus; PFS: progression free survival; OS: overall survival; tox: toxicity; LTS: long term survival; TKI: tyrosine kinase inhibitor; TPS: tumor proportion score; pembro: pembrolizumab; NA: not available; TRAE: treatment related adverse events; nivo: nivolumab; NR: not reported; ipi: ipilimumab; ins: insertion; chemo: chemotherapy; TC: tumor cells; IC: immune cells; atezo: atezolizumab; durva: durvalumab; ALK: anaplastic lymphoma kinase; EAP: expanded access program

* Also including EGFR unknown; ~:7/8 EGFR-mutant patients EGFR TKI pretreated; ß:7 patients received previous erlotinib, 4 other targeted therapies, not specified according to EGFR-mutational status; Δ: only responses at first assessment mentioned; Σ: results cohort 1 summarized for DoR, PFS and OS as pooling was not possible; ∞: 1 patient both EGFR and ALK + .

exposed to ICI (non-reached vs. 21.1 months, p = 0.018) [87]. The results mirror those reported in the ImmunoTarget *BRAF*-mutant cohort (n = 43) with 24% RR and a median PFS and OS of 3.1 and 13.6 months, respectively (Table 1). In this study, neither *BRAF*-mutation subtype nor the number of previous lines impacted PFS, but rather smoking habits, while no data on the correlation with PD-L1 expression was provided [35].

In view of these results, ICI may play indeed a role in the therapeutic landscape of *BRAF*-mutant NSCLC patients regardless of predictive biomarkers and *BRAF*-mutation subtype. It remains unknown though, whether combining immunotherapy and double *BRAF-MEK* inhibition might improve outcomes considering the high response rates of targeted therapy and the durability of responses obtained with immunotherapy. It is nevertheless important to note, that improved antitumor activity of immunotherapy with *BRAF* and *MEK* inhibitors has been already described using syngeneic *BRAF*(V600E)-driven mouse models in melanoma [88].

MET mutation

The mesenchymal epithelial transition factor receptor (*MET*) gene is located on chromosome 7q21–q31 and its oncogenic function in lung cancer, occurs through its dysregulation via a variety of mechanisms, including gene mutations (mainly occurring in exon 14 [ex14]) or amplification (both reported in 3% of lung adenocarcinomas), rearrangements, and protein overexpression [89–91]. *MET* ex14 splicing mutations are common in older patients and more likely associated with smoking compared to other oncogenes [92], and is found enriched up to 22% in sarcomatoid histologies [93]. Although both *MET* ex14 splicing mutation and *MET* amplification, predict worse survival [91], they promote sensitivity to MET-inhibitors with RR about 40% in patients treated with crizotinib [94,95]. Based on the results, the FDA

Table 4
Clinical trials combining EGFR TKI and immunotherapy: response rate and toxicity.

Trial	Type and number included patients*	TKI, dose	ICI, dose	ORR (%) in dose expansion cohort	DoR (in dose expansion cohort)	Median PFS	Median OS	Grade ≥ 3 TRAE (safety and dose expansion cohorts)
TATTON [133]	A: *EGFR* + PD on EGFR-TKI n = 23 B: *EGFR* + EGFR-TKI naive n = 11	Osimertinib 80 mg QD	A: durva 3 mg/kg iv/durva Q2Q 10 mg/kg iv Q2W B: durva 10 mg/kg iv Q2W	70	45–80 days	NA	NA	47% 15% pneumonitis
NCT 02,088,112 [134]	A: ≤ 4 lines of tx n = 10B: *EGFR* + EGFR TKI naive n = 20	Gefitinib 250 mg QD A: arm 1 no run in, arm 2 run in	A: Durva 3 mg/kg iv Q2W/ durva 10 mg/kg iv Q2W B: durva 10 mg/ig iv Q2W	79	NA	NA	NA	50% Mainly liver
CheckMate 012 [135]	*EGFR* + n = 21, 20 TKI pretreated	Erlotinib 150 mg QD	Nivo 3 mg/kg iv Q2W	15 (TKI pretreated) TKI naive: 1 patient with CR	12.5–38.2 months TKI naïve > 5 year	5.1 TKI naïve > 5 year	18.7 TKI naïve > 5 year	24% Mainly liver/diarrhea
NCT 02,013,219[136]	A: NSCLC n = 8 B: *EGFR* + EGFR TKI naive n = 20	Erlotinib 150 mg QD 7 day run in	Atezo 1200 mg iv Q3W	75	9.7 months	11.3 months	NA	39% Mainly pyrexia and liver
GEFTREM[137]	*EGFR* + PD on EGFR-TKI (+/− chemo) n = 26	Gefitinib 250 mg QD 2 week run in	Tremelimumab 3–6–10 mg/kg iv Q4W (maintenance Q12W)	0	NA	NA	NA	54% Mainly diarrhea

Abbreviations: TKI: tyrosine kinase inhibitor; ICI: immune checkpoint inhibitor; ORR: objective response rate; DoR: duration of response; PFS: progression free survival; OS: overall survival; TRAE: treatment related adverse events; EGFR: epidermal growth factor receptor; PD: progressive disease; n: number; QD: once daily; durva: durvalumab; mg: milligram; iv: intravenous; QXW: every X weeks; NA: not available; tx: treatment; R: complete response; nivo: nivolumab; atezo: atezolizumab.
* A: dose escalation; B: dose expanding.

approved on May 2018, the use of crizotinib for the treatment of *MET*-mutant NSCLC patients.

Recent data provides more insights about the immunophenotype of *MET*-driven NSCLC. In preclinical models, *MET*-signalling activation promotes a transcriptional increase of several negative checkpoint regulators of the immune-response such as PD-L1, suggesting that an immunosuppressive environment is one of the oncogenic features of *MET* [51]. Expression of PD-L1 in *MET* ex14 NSCLC tumor samples is frequent, with almost 44% of tumours expressing levels ≥50% (by E1L3N clone), but unlike in the unselected population, median TMB is significantly lower (5.7 vs. 3.8 Mut/Mb, p = 0.0006) [38,46]. In a small cohort of 63 patients with *MET* ex14 skipping NSCLC, time on therapy with ICIs ranged from 2 weeks to 9.6 + months and overall RR was 13%, though somehow increased in those patients with higher levels of PD-L1 ≥ 50% (33% vs. 20% in patients with PD-L1 0%, respectively) [38]. These results mirror those reported in ImmunoTarget cohort among 36 *MET* ex14 skipping NSCLC (42% PD-L1 positive) with a RR of 16% and median PFS and OS of 3.4 months and 18.4 months, respectively [35].

As such, it is evident that despite frequent PD-L1 expression, responses to immunotherapy in *MET* ex14 NSCLC patients are globally uncommon and lower than that observed with targeted therapy. There is, therefore, a clear need for further exploration to unveil the underlying mechanisms of immunotherapy resistance in this defined subset of PD-L1 expressing tumors.

HER2

HER2 alterations, including *HER2* mutations and *HER2* amplifications are found in approximately 2–6% and 2–5% of lung adenocarcinomas, respectively. In addition, high level (3+) HER2 protein overexpression by IHC occurs in 2–4% of lung cancers. *HER2* mutations are not associated with *HER2* amplification, thus representing distinct clinical entities and therapeutic targets [96]. *HER2*-mutations are more common in adenocarcinoma, women and non-smoker population [97], in contrast to *HER2* amplifications which are more common in male and former smokers [96]. The ado-Trastuzumab emtansine (T-DM1), is an antibody-drug conjugate that has showed preliminary promising activity in *HER2*-mutant lung tumours but otherwise unsatisfactory for patients with *HER2*-positive lung cancer [98]. As no personalised targeted therapy has yet been approved, chemotherapy remains for the time being the core treatment option in this population of lung cancer patients [99].

The landscape of PD-L1 and TMB in this subset of lung cancers as well as their sensitivity to ICI is largely unknown. Recently, PD-L1 expression (E1L3N clone) and TMB (by NGS) has been studied in a large cohort of 122 *HER2*-mutant NSCLC patients. Notable among these, PD-L1 expression levels were lower (only 13% of patients had PD-L1 ≥ 50% and 77% of samples with PD-L1 < 1%) but TMB was similar to unselected lung cancers (median TMB 5.7 Mut/Mb) [100]. Among 26 *HER2*-mutant patients who received ICIs, RR was uncommon with only 12% (including 3 partial responses, two of them reporting high PD-L1 ≥ 50% and TMB above the median). The median PFS and OS were also poor; 1.9 months and 10.4 months, respectively [100]. In 29 *HER2*-positive NSCLC patients enrolled in ImmunoTarget cohort, outcomes were consistently poor (RR 7% and PFS and OS of 2.5 and 20.3 months respectively), but they did not gather data regarding expression level of PD-L1 (27% PD-L1-posiitve) or TMB [35] (Table 1).

Although activity of ICI seems to be poor in patients with *HER2*-altered lung cancers, treatment with ICI might be still be considered, particularly in the context of high PD-L1 expression or TMB. However, it is advised that data on ICI activity here reported is based only on small series of patients, so larger-scale validations are needed to sustain these observations.

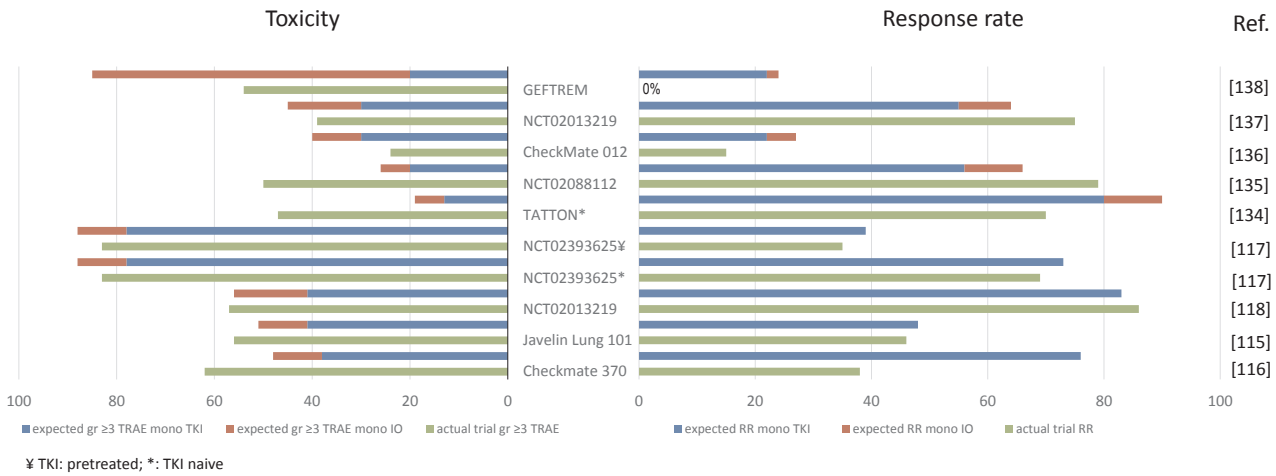

Fig. 1. Toxicity and efficacy (response rate) in *EGFR*-mutant and *ALK*-positive NSCLC patients treated with TKI with and without immunotherapy. Monotherapy data RR: gefitinib: Paz-Ares Ann Oncol 2017; tremelimumab: Maio Lancet Oncol 2017; erlotinib: Rosell Lancet Oncol 2012; atezolizumab EGFR: Rittmeyer Lancet 2017; erlotinib TKI pretreated: Capuzzo Lung Cancer 2017; nivolumab EGFR: Borghaei NEJM 2015; durvalumab EGFR: Garassino Lancet Oncol 2018; osimertinib: Soria NEJM 2018; ceritinib: Shaw Lancet Oncol 2017; nivolumab ALK+: Mazieres ASCO 2018; alectinib: Peters NEJM 2018; atezolizumab ALK+: Mazieres ASCO 2018 (no specific atezolizumab data available for ALK); lorlatinib: Solomon WCLC 2017 data exp4 and 5 combined; avelumab ALK+: Mazieres ASCO 2018. Monotherapy data gr ≥3 TRAE: same studies as for RR, except when AE instead of TRAE where reported in these studies, then replaced by studies with TRAE available: ceritinib: Soria Lancet 2017; crizotinib Blackhall ESMO open 2017. All cause AE instead of TRAE (TRAE not availabe: ceritinib and alectinib monotherapy, Javelin Lung, NCT02393625.

ALK rearrangements

ALK rearrangements result from inversions or translocations on chromosome 2 and are present in ~5% of NSCLC tumours [41,77]. Its phenotype is not linked to any ethnic group, but it is more commonly found in never/light smokers, young patients and adenocarcinoma subtype with either signet-ring or acinar pattern. This population experiences a remarkably long OS, up to 7.5 years, when sequential ALK inhibitors are prescribed [101]. Based on the positive results of different phase III clinical trials, several ALK inhibitors have been already approved in first-line setting by both EMA and FDA (crizotinib according to PROFILE 1014 trial [102,103], ceritinib based on the ASCEND 4 trial [104], and alectinib based on the ALEX trial [105,106]). In first-line setting, ALK inhibitors have outstanding activity with overall RR ranging from 73% to 83%, median DoR from 11.3 to 33.3 months, PFS of 10.9 months to 34.8 months and variable toxicity (grade ≥ 3 adverse events [AE's] 45% to 78%). In crizotinib-refractory *ALK*-positive NSCLC patients, several inhibitors have also shown to retain notable activity; among them ceritinib (ASCEND 5 phase III trial [107]), alectinib (NP28673 and NP28761 phase II trials [108]), brigatinib (ALTA phase II trial [109,110]), ensartinib [111], and lorlatinib in a phase II trial [112]. Currently ceritinib, alectinib (FDA and EMA) and brigatinib (FDA) have been granted market authorization in crizotinib-refractory patients.

As observed in other driver alterations, PD-L1 expression is remarkably increased with over-expression of ALK fusion protein [58]. TPS scored as ≥1%, ≥ 5%, and ≥50% is found in 63%, 47% and 26% ALK-naïve tumor samples (N = 19), and in 42%, 25% and 17% in ALK-resistant biopsies (N = 12) [45]. and PD-L1 TPS score ≥50% can reach 57.1% in heavily pretreated ALK samples [64]. However, TMB in this population is significantly lower (mean 3.1 mutation/Mb) than found in unselected NSCLC patients [28].

In vitro, PD-L1 mediated by *ALK* fusion protein induces apoptosis of T cells and treatment with ALK inhibitors can reduce PD-L1 expression and reverse T cell suppression [113]. Although in co-culture models, ICI is effective in both crizotinib-sensitive and -resistant *ALK*-positive cell lines, no synergistic tumor killing effects are observed by combining ALK inhibitors and ICI, probably due to the enhanced antitumor immunity induced by ALK inhibitors via the downregulation of PD-L1 [113]. Notwithstanding, preliminary data of ICI efficacy in *ALK*-positive NSCLC patients included in prospective trials (ATLANTIC) [71], as well as in retrospective cohorts of patients [45], such as the ImmunoTarget cohort [35], (Table 1) is deeply discouraging, with no responses observed, calling into question the role of ICI in these subset of oncogenic tumors. In the previously reported IMPOWER 150 phase III trial, 34 *ALK*-positive previously treated advanced NSCLC patients were enrolled. In the *EGFR/ALK* cohort, PFS and OS was longer in the combination arm with atezolizumab compared with the control arm [10], so this combination could be a potential therapeutic strategy in selected *ALK*-positive NSCLC patients who have become refractory to all ALK inhibitors available.

The next step was therefore to explore new combinations of targeted therapy with immunotherapy with the hypothesis that this approach could result in more responses and/or more durable responses in *ALK*-positive patients (Table 5). The phase Ib JAVELIN Lung 101 trial evaluated the combination of avelumab (10 mg/kg Q2W) and lorlatinib (100 mg QD) in previously treated *ALK*-positive patients (n = 28), as well as the combination of avelumab (at the same dose) plus crizotinib (250 mg BID) in ALK-negative NSCLC patients (n = 12). The primary endpoint was dose-limiting toxicities (DLTs); secondary endpoints included AEs and ORR. In the *ALK*-positive cohort asymptomatic and untreated brain metastases were allowed (36%) and most patients

Table 5
Efficacy of ALK TKI in combination with immune checkpoint inhibitors in treatment naïve or refractory NSCLC patients.

	Javelin Lung 101 Avelumab Lorlatinib [114]	Alectinib Atezolizumab [117]	CheckMate 370 Crizotinib Nivolumab [115]	Ceritinib Nivolumab [116]	
N	28	21	13	16	20
Line	Pre-treated	Naïve	Naive	Naïve	Pre-treated
RR (%)	46.4	86	38	68.8	35
DoR (mo.)	7.4	20.3	NR	14.9	11.9
PFS (mo.)	NR	21.7	NR	16.6	4.6
AEs Gr ≥ 3 (%)	56.4	57.1	62	83	

PFS: Progression free survival. OS: Overall Survival. RR: response rate. N: number. DoR: duration of response. AEs: Adverse Events.

(71.4%) were heavily pretreated with ≥2 previous ALK inhibitors. No data about PD-L1 expression in any of both cohorts were reported. The RR and the DoR were 46.4% and 7.4 months in the *ALK*-positive cohort and 16.7% and 4.1 months in the ALK-negative cohort, respectively. The toxicity of the combination was significant and comparable in both cohorts, with grade ≥3 AE's in the range between 54 and 58% [114]. Due to the dismal outcomes and the high rate of AE's, further development of this combination in the *ALK*-negative cohort was withheld, and although in heavily pretreated *ALK*-positive NSCLC patients the combination seems to be active, the outcomes achieved did not differ much from the ones observed with lorlatinib monotherapy (RR 39%, median DoR 7 months in previously pre-treated ALK-positive NSCLC patients) [112] but with the drawback of higher toxicity.

But, toxicity concerns have also arisen with the use of other combinations. The phase I CheckMate 370 trial evaluated in a single arm-cohort (group E) the safety of nivolumab (240 mg Q2W) plus crizotinib (250 mg twice daily) in TKI-naïve *ALK*-positive patients [115]. The enrolment was early terminated, as the primary endpoint (20% treatment discontinuations due to treatment-related AEs by week 17) was not met in the first planned safety review. Eight patients (62%) developed grade ≥3 AE's including five patients (38%) who developed severe hepatic toxicities with two possible related deaths. The rates of discontinuations due to liver toxicity reported in this trial greatly exceed those reported with nivolumab (0.3–1.5%) or crizotinib (2.3%) as monotherapy suggesting either a toxicity overlap or a synergistic result of the combination [115].

In another phase I trial, TKI-naïve (n = 16) and previously treated (n = 20) ALK-positive NSCLC patients, received nivolumab 3 mg/kg IV Q2W plus ceritinib with low-fat meal, at 450 mg/day (group 1) or 300 mg/day (group 2) [116]. The RR, DoR and PFS were of 69%, 14.9 months and 16.6 months among treatment-naïve patients and 35%, 11.9 months and 4.6 months, in previously treated patients. Once again, grade ≥3 AE's were commonly reported in 83% of cases, leading to dose interruption and discontinuation in 64% and 22% of patients respectively. Hepatotoxicity was the most common AE (all grades 69% and grade 3 elevation of ALT 25%) and grade ≥3 rash occurred in 19% of patients [116]. The preliminary efficacy results led to an amendment to address observed toxicities and to further evaluate an alternative dosing regimen with an induction period of ceritinib monotherapy followed by the combination. Despite the activity of the combination, it is worth highlighting that the results did not improve the outcomes achieved with ceritinib monotherapy, neither in first-line [104] nor in crizotinib-refractory patients [107], yet with a detrimental tolerability.

Lastly, the combination of alectinib and atezolizumab has been also studied in another phase Ib trial including 21 treatment-naïve *ALK*-positive NSCLC patients (28.6% with asymptomatic baseline brain metastases, and 53% PD-L1 positive by SP142). Patients received induction alectinib 600 mg BID for 7 days (safety evaluation), followed by alectinib 600 mg BID in combination with atezolizumab 1200 mg IV q3w (expansion stage) until progression or unacceptable toxicity [117]. At a median follow up of 16.9 months, the RR, DoR and PFS was 86%, 20.3 and 21.7 months, respectively. Toxicity was again noteworthy, with 66.7% grade 3 AEs (57.1% treatment-related, mainly rash and liver toxicity) and 33% serious AEs, though no grade 4–5 AEs were reported. Bearing in mind the impressive updated PFS of 34.8 months results obtained with first-line alectinib in the phase III ALEX trial [106], it does not seem that the combination of alectinib and atezolizumab is adding any outcome advantage in this subgroup of patients.

Taking together all previous data, it is conceivable that combinations of ALK inhibitors and ICI increase hepatotoxicity rates. Although hepatotoxicity is a class-effect related to of ALK inhibitors, the mechanism of action for increased toxicity observed by combining both treatments remains still unknown. Despite the discouraging above-mentioned results, there are still several ongoing clinical trials testing the efficacy and safety of combination strategies (NCT01998126, NCT02511184, NCT02898116), however, to our knowledge, preliminary results have not yet been reported.

ROS1 rearrangement

ROS1 rearrangements incidence in NSCLC range from 0.9 to 2% and, as is the case of *ALK*-positive tumors, are associated with younger age, never or light smoking history and adenocarcinoma histology [118]. However, compared to *ALK*, *ROS1*-positive NSCLC patients have different patterns of spread with significantly lower rate of extra-thoracic metastasis including fewer brain metastasis during the course of the disease [119]. So far crizotinib is the only *ROS1* inhibitor approved by FDA and EMA [120,121], although there is cumulative data suggesting that others such as ceritinib [122], entrectinib [123] or lorlatinib [112], might be as well active in this oncogenic-driven disease.

Much less data exist for *ROS1*-positive NSCLC patients regarding its immunophenotype. Although the high homology between *ALK*- and *ROS1*- kinase domains might suggest a similar pre-clinical effect on PD-L1 expression, high PD-L1 TPS in *ROS1* has been rarely reported [36].

A retrospective Korean *ROS1*-positive cohort (n = 12) treated with ICIs, reported RR of 25% and median PFS and OS of 1.6 and 23.4 months respectively. The majority of patients presented lung progression and data about PD-L1 expression was not reported [124]. In the ImmunoTarget cohort, seven *ROS1*-positive NSCLC patients were enrolled with RR of 17% but no data on PFS and OS was reported [35] (Table 1). These results seem rather better than those reported with durvalumab in *ALK*-positive NSCLC patients, and similar to that of wild-type population.

RET fusion

RET is encoded by the proto-oncogene *RET* located at chromosome 10, and its oncogenic activation can occur by two primary mechanisms: rearrangements and mutations, although only the latest has been described in NSCLC (1–2% of lung adenocarcinomas and 14% in enriched wild-type patients). In NSCLC, at least 12 fusion *RET* partners genes have been identified, being the most common the *KIF5B-RET* found in 75% of cases [125]. *RET*-rearranged NSCLC tumours are potentially sensitive to chemotherapy, particularly pemetrexed-based regimens. In terms of prognostic value, *RET*-rearrangement does not significantly correlates with OS and should not be considered a negative prognostic-factor [125]. Two selective RET inhibitors show promise as new potential standard strategies in RET-positive tumors; LOXO-292 [126] and BLU-667 [127], both achieving RR beyond 60% in *RET*-positive NSCLC patients.

PD-L1 expression (by E1L3N clone) is present in a substantial proportion of *RET*-positive lung adenocarcinoma (42%, 25% and 21% using TPS of ≥0%, 1–49% and 50%, respectively) [128] and the median TMB (by NGS) is significantly lower (3.3 Mut/Mb) compared to unselected NSCLC patients.

While PDL-1 is commonly expressed, responses to ICI, as observed in other drivers, are poor. Recently, a small retrospective cohort (n = 12) of *RET*-positive NSCLC patients treated with ICI, has reported RR of 0% with a median DoR of 1.4 months, responses that were otherwise not enriched by selecting those patients with positive PD-L1 expression or high TMB. Moreover, the median OS did not differ between those *RET*-positive patients exposed to ICI and those who did not (18.2 vs. 17,9 months p = 0.6) [129]. These results do not differ much from those reported in the ImmunoTarget cohort (RR of only 6% and a median PFS and OS of 2.1 and 21.3 months, respectively) [35], (Table 1). Therefore, thus far, ICI should not be offered as first-line treatment in this population and *RET*-directed targeted therapy strategies and platinum doublet chemotherapy should be considered prior to any single-agent immunotherapy. It remains unknown however, whether the use of combinations of *RET*-selective inhibitors and ICI might improve outcomes in this selected subset of patients.

Conclusions

Although ICI has been a major breakthrough in lung cancer treatment, the value on specific subsets of oncogenic driven tumors remains uncertain. Overall, data from several trials and those reported in the ImmunoTarget, point out towards the remarkably inferior activity of ICI to that achieved with targeted agents in some oncogenic-driven tumors. However, the very restricted number of patients evaluated and the little information regarding biomarkers of immune-response such as TMB or PDL-1, hamper the identification of the subgroup of patients, if any, that might derive greater benefit from this therapeutic approach. Combination of target therapies and ICI do not seem to improve outcomes yet with a detrimental tolerability and an increased rate of (hepatic) toxicity. As PD-L1 expression and an immune-suppressive microenvironment are constitutive and not an adaptive feature of several oncogenic-tumors, it is feasible that TMB may play a most relevant role in oncogenic addicted tumors rather than PD-L1 expression itself, however, it merits further evaluation in large prospective cohorts.

Further evaluation focusing on the study of biomarkers is needed in this selected population of oncogenic-driven lung cancer patients to identify those that might derive the greatest benefit. Meanwhile, treatments with ICI in this subgroup of patients deserve careful consideration and must be only used after exhaustion of other active targeted treatments.

Conflicts of interests:

The authors declare don't have any conflict of interest.

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